Mineral Supplementation of Foods, Feeds

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SHOULD FOODS and feeds be supplemented with minerals and, if so, with what minerals and to what extent? Satisfactory answers to this multiple question can be given only after a great deal more evidence has been developed by the various disciplines related to nutrition. But while few categorical answers can be reached from available data, this should be only a partial deterrent to formulation of some tentative recommendations.

Mineral addition to foods and feeds can be accomplished directly or indirectly. Direct addition is exemplified by the present practice of supplementing wheat flour with iron. Indirectly the same end may be reached in some cases by addition of minerals to the feed of animals whose tissues may later serve as human food, or by specific fertilization to increase the mineral content of crops destined for either animal or human consumption.

A vexing problem in the matter of mineral additives involves the array of nutritional interrelations of various inorganic ions which may actually be deciding factors and may be partly or wholly unassessable, or even unknown.

Mineral supplementation must be considered in general terms covering populations of people or animals, or else in relation to a specific dietary situation; a conclusion satisfying the latter instance may be entirely unadaptable to the former.
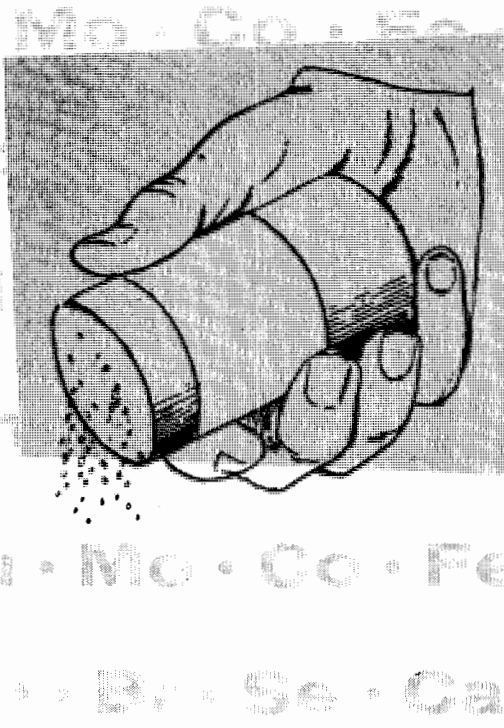
Calcium

Recommended dietary intakes of calcium for humans have been set by the Food and Nutrition Board of the National Research Council. In arriving at these recommendations many factors were considered, including data from various human calcium balance studies. Theoretically, balance study data should afford significant assistance in arriving at requirements. However, the validity of generalizing from data in specific calcium balance studies has recently been questioned.

Hegsted and coworkers (19) demonstrated from balance studies in man that the maintenance requirement for calcium is quite low in individuals who had subsisted over an extended period on low calcium intakes. In 10 adult men in Peru the average daily intake required to maintain equilibrium was 216 mg. of calcium.

Other balance experiments in adults who had subsisted on higher intakes might show maintenance requirements of two or three times this amount. Hegsted concluded that calcium balance experiments in adults bear no relation to requirements, but represent a study of calcium status related to previous intake (32). A large proportion of the world population of adults consumes far less than the recommended

allowance. Yet calcium deficiency symptoms in adults, reversible by calcium therapy alone, have not been described. The studies of Walker and coworkers with the Bantu population in South Africa (57) are of interest in this connection. These people have a sustained low calcium intake; yet they show no signs that might be attributed to a deficiency, nor the symptoms associated with known animal deficiency.

In children and adolescents where positive calcium balance is a prerequisite to growth, the requirement is higher. Whether the actual requirement approaches the recommended figure has been questioned principally on the grounds of: (a) the doubtful validity of balance studies in determining requirements, and (b) the mass experiment of observing the development of adolescents, most of whom have an intake less than that recommended. Again symptoms of calcium deficiency have not been defined in this age group.

During lactation most women are in negative calcium balance even when intake is markedly elevated. This is probably a normal physiological process; there is little evidence to indicate that attempts to obviate the negative balance are nutritionally sound.

From the foregoing it can be argued that recommended calcium allowances are higher than they need be. The extreme view in this regard was expressed recently by Walker (58), who questioned whether calcium should even remain in the Tables of Recommended Allowances. A more moderate view would be to suggest further downward revision of recommended intakes, especially for adults, in order to conform more nearly with nutritional practice and experience in the U. S. Supplementation of foods with calcium does not appear to be warranted.

Iodine

The control of simple goiter in this country through addition of iodides to the diet is an old story. The classic experiments of Marine and coworkers in Ohio as early as 1916 clearly demonstrated the efficacy of this treatment, and supplementation of table salt with iodides was soon shown to be practical. By 1925 manufacturers were adding potassium iodide to table salt, and health agencies were recommending its use in known goitrous areas.

A recent survey by Hamwi et al. (16) of some 27,000 Ohio school children was planned to determine the present incidence of enlarged thyroid glands, and to study the progress made since 1925 in controlling simple goiter. The 1954 survey was conducted in the same four counties in which Kimball had examined children in 1925 (unpublished data cited by Hamwi et al.), to increase the comparative value of the data. Criteria used in the examinations were similar in both surveys.

Table I, modified from Hamwi and coworkers, shows the incidence of enlarged thyroid glands found in 1925 and in 1954. The over-all decline in enlarged thyroids from 32.3% in 1925 to 4.0% in 1954 is due largely to the use of iodized salt, although other factors, such as increased availability of sea foods, are known to be involved.

It was calculated in 1954 that some 320,000 persons in Ohio would show some degree of enlarged thyroid gland. Thus endemic goiter remains a minor public health problem there, and further educational effort on the use of iodized salt and iodine-containing foods is required.

The use of iodized salt in livestock management surely rests upon an equally sound basis.

Copper

In 1928, Wisconsin workers announced that copper is essential with iron for hemoglobin regeneration in milk fed anemic rats (18). A controversy was maintained for several years on this point. Workers who used preparations of iron salts especially purified by the Wisconsin group, or who successfully removed copper from their own iron salts, corroborated this finding. Others who employed copper-contaminated iron preparations could not. But the essential nature of copper for various species was soon established; the early work has been reviewed by Elvehjem (11).

A number of instances of copper deficiency symptoms in grazing cattle and sheep were reported in the 1930's. Copper therapy was effective in the prevention of symptoms. Many areas are now known in which the pasturage is very low in copper, usually because this element is lacking in the soil.

Until recently many workers held that a human case of copper deficiency had not been clearly demonstrated (5). Some studies, however, have indicated a beneficial effect of copper along with iron in the maintenance of hemoglobin levels in infants, while in other studies hemoglobin response to additional copper was not found. Wintrobe and coworkers (6) found no hypocupremia in 24 infants with hypochromic microcytic anemia nor in repatriated war prisoners who had suffered from starvation, although they demonstrated decreased blood iron levels.

Infants fed for as long as five months on diets identical with those producing copper deficiency in young pigs developed no deficiency symptoms. It was suggested that the great difference in growth rate or in copper stores or in requirements of these two species might account for such findings (62).

In general iron deficiency anemia in infants is not associated with lowered blood copper concentration. In 1956 a report of five cases of what may be copper deficiency in infants appeared (49). The plasma copper level of normal 4-months-old infants was given as 100 μg per 100 ml. The five infants studied showed 24, 28, 37, 43, and 68 μg per 100 ml. These infants had subsisted on milk almost exclusively.

Oral copper sulfate corrected the hypocupremia, and an improved diet corrected the other symptoms as well.

A frank copper deficiency may exist in humans, but it must be exceedingly rare, and copper supplementation of foods is not justified at this time.

Anemia is an outstanding consequence of insufficient copper intake. But this is but one of many manifestations. In a deficiency state among the several animal species studied, copper

supplementation alleviates such other conditions as myocardial fibrosis, abnormal bone development, depigmentation of fur and wool, demyelination of the spinal cord, and lowered growth rate. Not all species exhibit all these symptoms, and in a given species the symptoms may not appear in a consistent order relative to time; their appearance is markedly influenced by age, degree and time course of the development of deficiency, and other dietary factors.

Only a beginning has been made toward understanding how copper deficiency actually leads to the various symptoms observed.

An example is found in studies on red cell formation in copper deficient pigs. Cartwright (5) has shown that there is a decreased red cell survival time and a concomitant rate of new cell formation insufficient to compensate for the increased rate of destruction.

A significant function of copper is related to iron absorption. In pigs deficient in copper but supplied with sufficient iron, severe anemia develops. In this type of animal Wintrobe and coworkers (62) withdrew the iron for a period of 5 days and then administered copper. No blood regeneration followed this treatment with copper. After another 5-day interval without copper, iron was given and rapid erythropoiesis ensued. This indicates that iron was absorbed only after the tissues were supplied with copper.

These workers also indicated that in copper deficient pigs the intravenous use of iron salts had no significant effect on anemia. This work with radio iron showed that even parenteral iron is unavailable for hemoglobin synthesis by copper deficient tissues in the pig.

It is also known that copper enzymes are involved in the oxidation of —SH groups of prekeratin to S—S groups of keratin in wool. Malfunction in this series of reactions probably causes loss of crimp in wool (25). Pigmentation of black wool is definitely hampered by copper deficiency, probably through interference with phenol oxidase enzymes involving tyrosine metabolism.

Of interest, also, is the demonstration by Mills (27, 28) that certain freeze-dried preparations of herbage fed to copper deficient rats gave consistently greater responses in growth, hemoglobin levels, and liver copper stores than did equivalent amounts of copper sulfate. After further treatment a residue was obtained containing combined copper which was effective at much lower levels than inorganic copper. The indication here is that certain soluble copper complexes are absorbed intact and are more active or available than cupric ion (33).

Included among the enzymes and proteins of mammalian tissues known to contain copper are tyrosinase, phenolase, uricase, ceruloplasmin, hepatocuprein, erythrocuprein, and cerebrocuprein. Ceruloplasmin is said to hold 90% or more of the plasma copper. It has weak peroxidase activity in vitro, but its function in vivo is not definite.

In March of 1958 Morrell and others (30) announced that ceruloplasmin could be separated into copper and apoenzyme and that the reaction is reversible in vitro. This finding is consistent with the theory that ceruloplasmin functions by reversibly releasing and binding copper at various sites in the organism, thereby aiding in the regulation of copper absorption and/or transport.

Unfortunately, it is difficult to relate decreased activity of specific copper enzymes to specific deficiency symptoms. This statement also holds for other metal enzymes with but few exceptions.

Many grazing areas are known in which the pasturage does not supply cattle and sheep with sufficient copper to maintain normal metabolism. An example is found in the work of Adams and Haag (1) who have recently reported on the copper content of whole blood and the corresponding plasmas of over 800 samples from cattle in Oregon.

In two areas of the state known to result in deficiency symptoms in grazing cattle, the blood copper levels were very low. By appropriate copper supplementation, deficiency symptoms were alleviated, and blood levels were restored.

Of special significance in this work was the demonstration that whole blood copper and plasma copper were approximately equal only in the vicinity of 1 μg per ml. At the lower level of 0.3 μg per ml. of whole blood, the corresponding plasmas contained only 0.13 μg per ml. Such an average difference takes on considerable significance in the evaluation of copper status in cattle grazing on deficient or marginal land.

Specific fertilization with copper salts is effective in combating deficiency, but not practical on many large ranges. Moving livestock to unaffected areas or administration of copper where practical has been successful.

Under most conditions copper supplementation for animal feeds is not required. Many exceptions to this statement can be pointed out. There are innumerable reports of beneficial results in animal feeding from trace
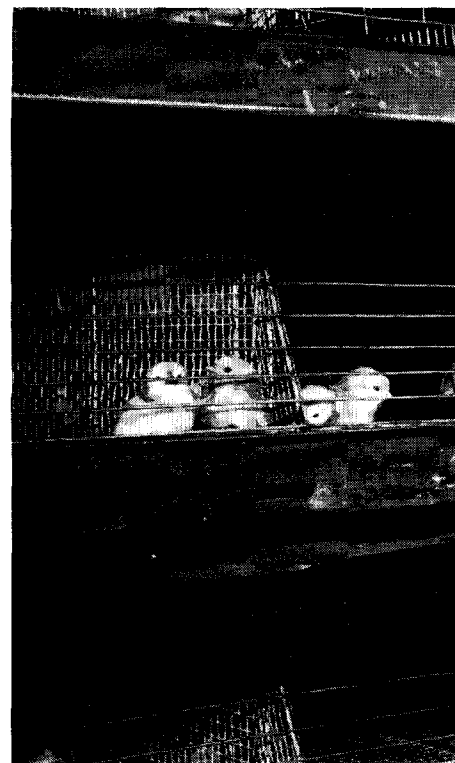
mineral supplementation containing copper, some of them involving the intriguing interrelations of copper, molybdenum, and sulfate.

Molybdenum

One of the early relations of molybdenum to nutrition was pointed out in 1938 when it was found that "teart" disease of cattle in parts of England was due to excess molybdenum intake from pasturage (13). It was demonstrated that herbage in such areas had molybdenum contents up to 300 p.p.m., dry basis, compared to 3 to 5 p.p.m. in healthful pasture areas. There soon followed experimental production of typical molybdenum toxicity symptoms in cattle by adding molybdate salts to otherwise nontoxic rations or by grazing cattle on healthful pastures to which molybdenum compounds had been applied (13).

The rapid amelioration of the debilitating symptoms in cattle of either normally or experimentally produced molybdenosis by oral or parenteral copper sulfate administration remains unexplained.

Also, elevated molybdenum intake limits absorption and storage of copper in the presence of sufficient dietary sulfate. The mechanism of this action is likewise obscure.

Demonstration in recent years of the profound effects of sulfate intake in relation to the copper-molybdenum axis makes it clear that previous animal work on this problem, in which sulfate intake was not considered, loses much of its significance (9, 63). Both molybdenum and sulfate in the
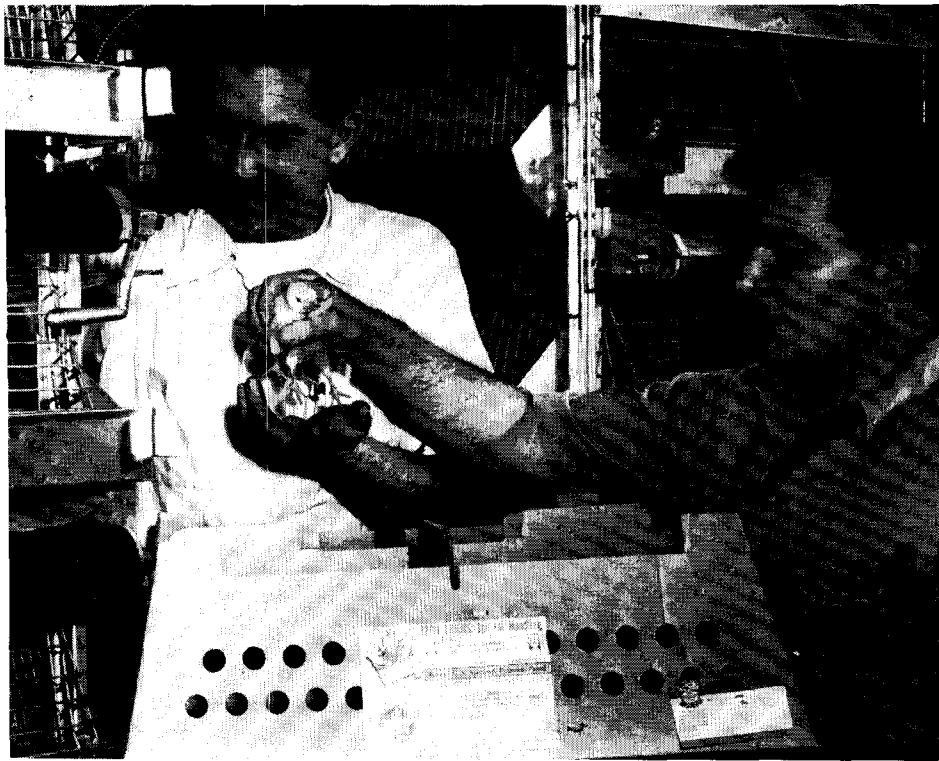
diet markedly suppress copper absorption, and the sulfate ion has the greater effect.

Manganese has been implicated in this already complicated picture by Dick (10), who showed that increased manganese intake in ruminants blocks the suppression of copper storage due to dietary sulfate and molybdenum, but that this odd effect does not occur after increasing dietary protein level.

The fact that sheep in some instances with excess molybdenum intake are known to maintain adequate tissue levels of copper for normal function, and still show signs of copper deficiency, could indicate that molybdenum is altering copper-protein chelates, or other types of attachment, so that one or more copper enzymes are no longer functional.

These examples are sufficient to indicate that our state of understanding in this field is not keeping pace with our state of knowledge. However, with further work designed on the basis of past experience, this situation will reverse itself. In the meantime the folly of indiscriminate mineral additives to human foods seems evident.

In 1953 two groups of workers announced that molybdenum is required in rat liver xanthine oxidase (8, 38). It is now known to be an essential part of the prosthetic group of this and two other flavoproteins, nitrate reductase of plants and microorganisms (31), and a hydrogenase of bacterial origin (44).

Deficiency symptoms in rats other than lowered xanthine oxidase activity have not been reported, although a growth response to added molybdenum in chicks and turkeys on purified diets indicates that the element must be considered for classification as essential (37) (see Table II).

Excess molybdenum in rats causes growth depression and marked increase of liver alkaline phosphatase activity. Extra dietary methionine, cystine, or sodium sulfate improves growth and lowers the elevated phosphatase activity. The amino acids may be active in this respect through conversion of sulfur to sulfate (56).

In man neither a dietary molybdenum toxicity nor deficiency has been reported. Molybdenum is probably essential in animal and human nutrition, but the complications and ramifications of its metabolic activities preclude, at this time, any recommendations regarding the use of this element as a food or feed additive.

Cobalt

Many areas of the world are now known to be deficient in cobalt to such an extent that cattle and sheep grazing these ranges develop a deficiency of this element. Various disease conditions including a severe anemia ensue and death may result if the diet is not corrected. In 1935 cobalt was demonstrated by Underwood and Filmer (52) to be the missing dietary factor in the wasting disease of sheep and cattle in Australia. Affected sheep were shown to respond in a dramatic fashion to small amounts of cobalt by mouth (24). Cobalt therapy was soon found to be highly effective in ruminants with similar deficiency symptoms in various parts of the world (25).

The simultaneous announcement of the isolation of vitamin B_{12} in 1948 by English (45) and by American workers (39) was of tremendous significance to nutrition workers, the medical profession, and pernicious anemia patients.

The relationship of this vitamin, containing about 4% cobalt, to cobalt deficiency in ruminants soon blossomed into a rather clearly defined picture. Some of the salient features of this picture are as follows:

(1) A cobalt deficiency in ruminants reflects a vitamin B_{12} deficiency. This is the only class of experimental animals in which a cobalt deficiency has been demonstrated.

(2) The vitamin is synthesized in nature only by certain microorganisms.

(3) Oral cobalt, but not parenteral cobalt, is dramatically effective in alleviating deficiency symptoms in cattle and sheep.

(4) B_{12} synthesis by rumen microorganisms depends upon the presence of sufficient cobalt; in a deficiency of this element the vitamin is not synthesized in sufficient quantity to maintain the supply required by the host.

(5) Parenteral administration of the vitamin is effective in a cobalt deficiency state.

Thus ruminants indeed require dietary cobalt, to supply microorganisms with the element so that they may synthesize vitamin B_{12} essential to the host. If cobalt has other physiological functions in these species, they have yet to be demonstrated.

In nonruminants, the picture is not so clear. It has been known for many years that cobalt salts given either orally or parenterally induce a polycythemia in man and experimental animals (40). The mechanism of this remarkable action has remained essentially unknown. Recently, however, it has been demonstrated that cobalt stimulates the production of erythropoieten, defined as a factor in plasma of anemic animals which accelerates erythropoiesis, or red corpuscle production, when injected into assay animals. Injection of cobaltous chloride brings about a very rapid increase in the blood titre of this "hormone," but again the mechanism remains obscure (14). The increase in erythropoieten as a result of cobalt intake may be involved in the development of polycythemia.

A further effect of cobalt involves its participation in the action of certain peptidase enzymes. Its action here appears to be on the basis of chelation with the substrate which in

Post mortem on an animal that died because of lack of manganese in diet

some way increases the availability of substrate for enzyme action (46).

An elemental cobalt deficiency has not been produced in nonruminant mammals. On a diet deficient in B_{12} the cobalt requirement is met probably by the minute quantity necessary for bacterial synthesis of the vitamin. It has so far been impossible to put together a ration for rats, pigs, or other nonruminants low enough in cobalt to elicit B_{12} or cobalt deficiency symptoms. This difficulty is related to the wide distribution of cobalt, and to the markedly lower B_{12} requirement of nonruminants—an established fact that remains unexplained.

It has not been demonstrated that any species requires cobalt beyond that needed for B_{12} synthesis, or contained in ingested B_{12}, nor that cobalt has other physiological functions in mammals than as a part of this vitamin.

Supplementation of feeds with cobalt or the use of cobalt-containing fertilizers on pasturage for cattle and sheep in affected areas has success-fully relieved the cobalt deficiency syndrome. There is no apparent need to consider supplementation of human food or the feed of other animals with this element.

Iron

Iron deficiency symptoms in man and animals are well known. Requirement of iron for the function of many enzyme systems in the body is established beyond doubt. Included among the iron-containing enzymes are the cytochromes, the catalases, the peroxidases, cytochrome reductase, cytochrome oxidase, xanthine oxidase, homogentisicase, hydroxyanthranilate oxidase, tryptophan oxidase, phenylalanine hydroxylase, and others (26). All of these enzymes are concerned with oxidation-reduction reactions involving activation of oxygen and/or electron transport. Other iron containing molecules in the body besides hemoglobin and myoglobin are ferritin, hemosiderin, and siderophilin.

The latter three iron-protein complexes operate in the absorption, storage, and transport of iron (15).

Beal (2) presented intakes of iron, among other minerals, of a small group of children during the first five years of life. He concluded that 75% of the children between the ages of two and a half and five years had intakes below the Recommended Allowances of the National Research Council, and that these intakes were not necessarily inadequate. This belief is not widely held, however.

Iron balance studies have limited value because of restrictive technical difficulties. But use of radio iron has enabled recent workers to study absorption, retention, excretion pathways, and requirements. In some instances these studies were conducted with food containing naturally combined Fe^{59} and thus are of particular interest (29).

These studies showed that in normal adults, iron absorption was invariably 10% or less of the amount taken; in iron-deficient patients the absorption was over 10% in the majority of cases. The simultaneous ingestion of ascorbic acid increased absorption markedly in normal people and to a greater extent in iron deficiency states.

In studies with bread prepared from flour enriched with Fe^{59} the absorption varied from 1 to 12% in a group of normal adults, from 26 to 38% in four individuals thought to have had suboptimal iron stores, and from 45 to 64% in three patients with frank iron deficiency anemia (47).

From experimental work and calculated estimates Steinkamp and co-workers (47) concluded that adult men consuming 12 to 15 mg. of food iron per day should readily maintain balance. But women are in a less favorable position because of menstruation and childbirth, and so a lowered intake or decreased absorption, or both, may lead to a deficiency state. From infancy to 20 years of age the net positive balance required was calculated to be 0.35 to 0.6 mg. per day. Again, with abnormalities in intake, absorption, or excretion, iron deficiency states may readily develop.

Supplementation of flour with iron is nutritionally sound, and study of further supplementation of foods should be continued.

In farm animals, nutritional iron deficiency is limited pretty much to young pigs. The iron content of the newborn pig is low in relation to other species; it cannot be increased significantly by supplementing the sow's diet with iron during gestation, nor can the sow's milk be strengthened in this element by feeding (17). For very rapid growth, a suckling pig requires about 7 mg. of iron per day. Only about 1

mg. is supplied by his daily quota of milk.

Anemia of young pigs is associated with clean pens and lack of access to soil or pasture. Wherever practical approaches to correct the iron deficiency have been instituted, the problem has ceased to exist. Providing soil in the pens, providing pasture for rooting, administration of iron salts to the young pigs orally or by implantation, and painting the sow's belly with iron salt solutions have all been used successfully.

In other farm animals, frank iron deficiency must be rare. Deficiency states reported for cattle and sheep grazing on low-iron forage have been adequately demonstrated to result from a lack of copper or cobalt or both.

Manganese

The first satisfactory demonstration of an essential role for manganese in animal nutrition was given by Hart and coworkers in 1931 (21). The Wisconsin group showed that in manganese deficiency there was impairment of growth and ovarian activity in rats. McCollum (35), in the same year, reported that on manganese-deficient diets female rats failed to suckle their young, and male rats showed testicular degeneration by the 100th day. There followed the clear-cut demonstration by Wilgus and others (60) that perosis in chicks was prevented by additions of manganese salts to the diet, although it is equally clear that other factors such as choline and inositol are interrelated in this metabolic disorder.

Many plant and animal enzymes are known to be activated by manganese ions. Among these are arginase, phosphoglucomutase, phosphomonoesterase, pyrophosphatase, certain of the dipeptidases, isocitric dehydrogenase, hexokinase, and various decarboxylases. Other bivalent metal ions can activate certain of these enzymes, but in some instances manganese is thought to be specific and indeed, essential for enzyme action.

In manganese deficiency there is a marked decrease in liver arginase activity and in liver manganese content in some species. Upon addition of the metal ion to liver preparations, activity can be substantially increased. But, as is so frequently the case, it is not possible to relate decreased enzyme activity resulting from low manganese intake to well known animal symptoms of deficiency such as those involving bone growth and reproduction.

Phillips and others (3) were able to develop deficiency symptoms in cattle fed natural rations of man-

ganese-low hay and various corn products, which are also comparatively low in this element. Reproductive performance was improved by manganese supplementation. This ration contained 7 to 10 p.p.m. manganese on the dry basis. Thus, at least under these conditions, the requirement of cattle is something above this amount.

In suckling pigs a variety of deficiency symptoms appeared on diets very low in manganese (0.5 p.p.m.); other pigs on the same ration supplemented with the element to the extent of 40 p.p.m. exhibited none of the symptoms. One cannot determine from these data whether 20 or 10 p.p.m. would be effective. In weanling pigs, diets containing 0.5 to 3.5 p.p.m. of manganese did not elicit deficiency symptoms over the course of the study (36). The marked difference in response to low manganese intake of the two age groups of pigs must be related to other factors, as yet not clearly defined, in the two separate studies.

The practice of adding manganese to poultry rations is well established. Chickens, for instance, are fed largely on grain products, lower in manganese than are most range crops. The requirement is higher for chickens than for some other species, also (55). Use of manganese as an additive may also be sound in the feeding of pigs.

In man a deficiency of manganese has not been reported. A few balance experiments in humans indicate intakes but not requirements of manganese (22). One estimated requirement of 3 to 5 mg. per day for a 35-lb. child appears high (12), and not easily met without sizable amounts of high manganese foods in the diet.

The addition of manganese to poultry feed is based on sound evidence. Manganese as an additive to other feeds, except perhaps for pigs, appears unnecessary except in isolated localities. No evidence at this time indicates a need for addition of the element to human dietaries.

Zinc

In the early 1930's the Wisconsin workers offered the first clear-cut evidence that zinc is essential in the rat (50). Later work with improved diets demonstrated that mice do not survive on extremely low zinc intake (7).

Direct experimental evidence for such a requirement in other species including man seems unnecessary in view of the known relations of this metal to the enzyme carbonic anhydrase, essential in life processes. The observations of Vallee and coworkers on the functional aspect of zinc in

several dehydrogenases (53) and in pancreatic carboxypeptidase (54) indicate more diverse functions of the element than were previously assumed.

The low order of toxicity of zinc from the nutritional standpoint is well established (51). This is fortunate since the metal finds effective use in various food and feed handling equipment.

It is clear that the absence of zinc deficiency symptoms in man and animals under normal conditions is related to the abundant distribution of the element in soils and plant and animal tissues.

The requirement of zinc as adduced from the few studies available in man and animals is not great, and appears to be well met by diets supplying other essential nutrients.

Certain interrelations of some minerals in nutrition appear obscure and even odd to scientists at this time. Unless or until something of this nature is brought to light involving zinc, addition of it to human foods appears to be unnecessary.

However, the demonstration of parakeratosis and lowered growth rate in swine on certain rations, and the correction of these deficiency symptoms by addition to the diet or by injection of zinc salts focuses attention on zinc deficiency in this species. The relation of high calcium intake, but not of increased phosphate intake, to the development of symptoms is clear from several reports (34). The demonstration that these zinc deficiency symptoms do not develop in swine on purified rations but do on practical rations, although the calcium content in both may be very similar, clearly indicates that the elevated calcium intake is not the only factor involved in interrupting normal zinc metabolism.

The high zinc requirement of swine on some practical rations (up to 80 p.p.m.) is readily met by addition of
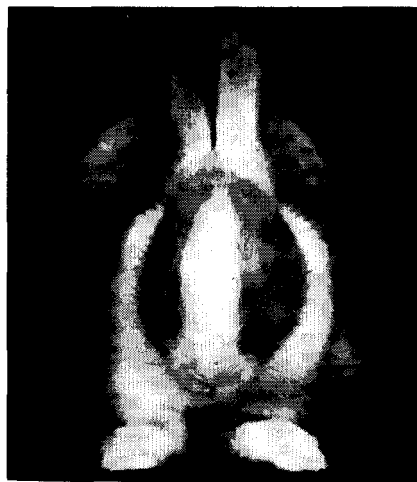
Rabbit's crooked, splayed legs are result of manganese deficiency

zinc salts; this addition must be made if deficiency symptoms are to be obviated.

Bromine

It is rather generally appreciated that the bromine content of most plant and animal tissues is far greater than the iodine content. Little work has been reported until very recently to indicate that this is anything but a fortuitous situation.

Growth retardation in mice was produced by feeding a synthetic diet supplemented with physiologically active iodinated casein and succinyl-sulfathiazole. Either the ash of whey, or trace element sea salt supplements reversed the growth inhibition. It was found that bromine was the active inorganic component. On diets devoid of essential fatty acids and containing iodinated casein, mice likewise showed a decreased growth rate. Huff and coworkers (20) showed that feeding linseed oil or sodium bromide partially prevented growth depression. The additive effect of bromide and linseed oil was shown by feeding them together, in which case no growth depression was evident.

The suggestion that the hyperthyroid condition evoked by iodinated casein increased tissue bromine requirements needs further exploration. Chicks on semisynthetic diets showed a slight increase in growth rate upon the addition of small amounts of sodium bromide. The effect was found in two hybrid strains, but not in an unidentified strain of New Hampshire cockerels (4). It was suggested that bromine carry-over in the egg might have accounted for the response failure in the one instance. Egg albumin contains a considerable quantity of bromine (61).

From the few data available, bromine appears to be required in two species of animals. These findings are of considerable academic interest since further details of metabolic pathways and mechanisms may evolve. Practical implications in feeding are not evident at this time.

Selenium

Toxic manifestations have been produced experimentally by feeding selenites, or have been brought on naturally in man and animals from diets high in selenium. But little recent work on the metabolic disturbances in chronic or acute selenium poisoning is available. It is known that selenium can replace sulfur in cystine, glutathione, and probably methionine. It is possible, according to Klug and coworkers (23), that this property is responsible for the reduction of succinic dehydrogenase activity in rats fed seleniferous diets, but it cannot be concluded that this accounts for the symptoms of selenium toxicity. One wonders about the relation of selenium to coenzyme A, since this molecule contains a sulfhydryl group.

Excess dietary selenium is not known to be an extensive public health hazard, but it is a matter of concern in animal husbandry in some parts of this country.

Of great interest is the announcement two years ago of the essential nutritional role of selenium. A deficiency disease characterized by liver necrosis in the rat was recognized in 1935 by Weichselbaum (59). Under various experimental conditions, Schwarz (41) was able to correct or prevent the debility by addition to the diet of vitamin E, cystine, or "factor 3" isolated from certain yeasts. Chickens develop exudative diathesis on vitamin E free rations containing torula yeast as the only source of protein. Vitamin E protects against the development of symptoms, and "factor 3" is likewise protective (43).

In 1957 Schwarz and Foltz (42) reported the presence of organically bound selenium in active preparations of "factor 3." Inorganic selenium was found to protect rats completely against the development of necrotic liver degeneration. Table III illustrates the minute quantities of selenium required for this protection, as well as the fact that tellurium and arsenic are inactive. The addition of 13.3 μg of sodium selenite per 100 g. of ration represents only 4 μg of the element. The quantity of selenium afforded one rat per day is thus a few tenths of one microgram. Schwarz and Foltz stated: "It can be inferred

Table I. Comparison of the Incidence of Enlarged Thyroid Gland in Ohio School Children as Shown by Goiter Surveys Made in Four Counties in 1925 and 1954

County		Total Cases Studied	% Goiter All Children
Butler	1925	10,679	31.5
	1954	12,905	3.0
Marion	1925	5,352	33.1
	1954	4,231	4.6
Union	1925	1,302	31.0
	1954	1,412	5.2
Washington	1925	4,247	33.8
	1954	3,854	5.9
Total	1925	21,580	32.3
	1954	22,402	4.0

Modified from Hamwi, G. J., coworkers, *Am. J. Public Health*, 45, 1344 (1955).

Table II. Effect of Minerals on Chick Growth

Supplement to Basal Diet	New Hampshire Chicks 4-wk. Avg. wt., g.	% Response over Basal
None	289.7	...
3% distillers dried solubles	376.7ᵃ	26.2
Distillers dried solubles ash equivalent to 3%	330.3ᵇ	14.0
Reconstituted ash equiv. 3% distillers dried solubles	335.2ᵇ	15.7
Molybdic acid, 0.0126 ppm Mo	344.0ᵇ	18.7

ᵃ Significant at 0.05 level of probability.
ᵇ Significant at 0.01 level of probability.
Table modified from Reid, B. L., Kurnick, A. A., Svacha, R. L., Couch, J. R., *Proc. Soc. Exptl. Biol. Med.*, 93, 245 (1956).

Table III. Effect Against Dietary Necrotic Liver Degeneration

Supplement	Salt mg./100 g. of Diet	Element μg./100 g. of Diet	No. of animals Total	Dead on 30th Day
None	...	...	18	17
Sodium selenite (Na$_2$SeO$_3$·5H$_2$O)	0.0199	6	10	0
	0.0133	4	10	0
	0.0067	2	10	3
	0.0033	1	5	4
Potassium selenate (K$_2$SeO$_4$)	0.280	100	5	0
	0.028	10	5	4
	0.003	1	5	4
Potassium tellurite (K$_2$TeO$_3$)	0.199	100	5	5
	0.020	10	5	5
Sodium arsenate (Na$_2$HAsO$_4$·7H$_2$O)	0.470	100	5	5
	0.047	10	5	5

From Schwarz, K., Foltz, C. M., *J. Am. Chem. Soc.*, 79, 3292 (1957).

from our results that selenium is an essential trace element." They suggested on the basis of certain other observations that selenium may function in oxidation-reduction reactions.

During 1957 two groups of workers reported that selenium added in minute quantities to diets known to produce exudative diathesis in chickens affords complete protection (43, 48). Again, the quantities shown to be effective were minute. These reports, together with others, undoubtedly will result in wide acceptance of selenium as an essential trace element.

At this time there seems to be no evidence of a need for increased selenium intake above the amounts occurring in natural vegetable and animal tissues.

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